PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Tsuyoshi NAGANUMA, et al.

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For: SOLID DRUG FOR ORAL USE

SUPPLEMENTAL DECLARATION UNDER 37 C.F.R. § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Tsuyoshi Naganuma, hereby declare and state:

THAT I am a citizen of Japan;

THAT I have received the degree of Bachelor of Science in Industrial Chemistry from Chuo University in 1990;

THAT I have been employed by Kissei Pharmaceutical Co, Ltd. since April 1990, engaged in engineering and research mainly on the production of drug products and formulation technology studies on drug products;

THAT I am one of the co-inventors of the invention disclosed in the above-identified U.S. patent application.

Further to the previously submitted Declarations to further demonstrate that the present invention is not obvious over Kitazawa in view of Ishihara and in further view of Salpekar and Shar, we conducted the following additional experiments.

Experiment

1. Preparation of Capsules of Examples 1, 2 and C of the present invention and comparative capsules N, O, B, H and Q

Capsules of Examples 1, 2 of the present invention and comparative examples N, O, B and H were prepared as described in the previous Declaration filed April 8, 2010.

Capsule C of the present invention was prepared as described in the previous Declaration filed July 22, 2009.

Comparative Capsule Q contains sodium lauryl sulfate as an intragranular ingredient and was prepared as described at column 4, lines 29 to 22 of Shar.

2. Dissolution Tests

In accordance with the procedures of "Dissolution Test Method" as described in Test Example 4 in the present specification, the capsules of Examples 1, 2 and C of the present invention and the comparative capsules N, O, B, H and Q were tested. The results are shown in Table 1.

3. Storage Stability Test

The capsules of Examples 1, 2 and C of the present invention and the comparative capsule Q were tested for storage stability under 60°C for 7 days. The results are shown in Table 1.

Comparing the granulated composition of capsules N and O representative of Shar with the capsule of the present invention, the granulated composition of capsules N and Odiffers from the granule of the present capsule in that the granulated composition of capsules N and O does not contain D-mannitol.

As shown in Table 1 the dissolution rates of Capsules N and O are notably lower than those of the Examples 1 and 2 of the present invention (the dissolution rate after 15 minutes: Capsule N: 0.6%; Capsule O: 32%; Example 1: 93%; and Example 2: 97%). In Table 1, Capsule B which corresponds to a capsule adding D-mannitol as an intragranular ingredient to Capsule N. The dissolution rate of Capsule B is also notably lower than those of the Examples 1 and 2 of the present invention (the dissolution rate after 15 minutes: Capsule B: 8%; Example 1: 93%; and Example 2: 97%).

A comparison of Capsules N, O and B with Examples 1, 2 and Capsule C shows that not only partially pregelatinized starch but also D-mannitol and sodium lauryl sulfate are necessary for imparting the immediate dissolution property.

Comparative Capsule Q, containing sodium lauryl sulfate as an intragranular ingredient as shown in Table 1 was prepared based on the description of Shar at column 4, lines 29 to 22. The granulated composition of Capsule Q contains at least a portion of lubricant as an intragranular ingredient as in Shar, while the capsule of the present contains lubricants as an extragranular ingredient. The dissolution rate of Capsule Q is considerably lower than that of Examples 1 and 2 of the present invention (the dissolution rates: Capsule Q 18% after 5 minutes, 67% after 15 minutes; Example 1: 75% after 5 minutes, 93% after 15 minutes; and Example 2:

77% after 5 minutes, 97% after 15 minutes). Furthermore, a storage stability test was conducted under 60 °C for 7 days with respect to Capsule Q. As a result, Capsule Q showed remarkable decomposition and was unstable while Examples 1 and 2 of the present invention exhibited excellent stabilities (the amount of decomposed product: Capsule Q: 7.44%; Example 1: 0.71%; and Example 2: 0.46%). These results show that sodium lauryl salfate is necessary as an extragranular ingredient for imparting immediate dissolution property and good storage stability.

The data shows that the combination of lubricant and sodium lauryl sulfate as an extragranular ingredient provides the capsule of the present invention with much higher dissolution properties as compared to capsules containing a lubricant alone. Further, the addition of sodium lauryl sulfate as an extragranular ingredient provides the capsule of the present invention with extremely higher storage stability as compared to capsules containing sodium lauryl sulfate as an intragranular ingredient.

Such advantageous effects of the present invention of decreasing dissolution time and increasing storage stability achieved by the combination of lubricant and sodium lauryl sulfate as an extragranular ingredient in the present invention are not taught or suggested and would not have been expected based on the teachings of the cited references whether taken alone or in combination.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States

Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 14-Feb.-2011

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Table 1

Capsule		The present invention			Comparative example					
	Ingredient	Example 1	Example 2	Capsule G	Capsule N	Capsule O	Capsule S	Capsule H	Capsule Q
	KMD-3213	2.0	4.0	4.0	4.0	4.0	4.0	2.0	4.0
	D-Mannitol	134.4	132.4	169.2			169.2	134.4	169.2
Intragranular ingredient	Partially pregelatinized starch (PCS)	26.0	26.0					26.0	
	Partially pregelatinized starch (Starch 1500)	9.0	9.0	10.0	10.0	10.0	10.0	9.0	10.0
	Sodium lauryl sulfate								1.8
Extragranular ingredient	Magnesium stearate	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
	Sodium lauryl sulfate	1.8	1.8	1.8		1.8			
total weight (mg/capsule)		176.0	176.0	186.8	15.8	17.6	185.0	173.2	186.8
Dissolution rate (%)	after 5 minutes	75	77	46				16	
	after 15 minutes	93	97	85	0.5	93	9	25	67
Storage stability	Amount of decomposed product (%)	0.71	0.46	2.81					7.44